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1 Drug description

Generic/Brand name:

Azacitidine/ Vidaza®

Developer/Company:

Celgene Corporation

Description:

Azacitidine (Vidaza ®), a new molecular entity, is a pyrimidine analogue with antineoplastic activity. Mechanisms of action include cytotoxicity on abnormal hematopoietic cells in the bone marrow and hypomethylation of DNA. Aberrantly methylated genes which are responsible for regulation of cell differentiation, death-pathways and cell-cycles, are believed to be re-expressed due to hypomethylation, leading to an uptake of cancer suppressing actitivities. Cytotoxic effects are exerted by incorporation and inhibition of DNA and RNA, resulting in an activation of DNA damage pathways [1].

mechanisms of action: cytotoxicity on abnormal hematopoietic cells and hypomethylation of DNA

The recommended treatment regimen consists of the subcutaneous injection of 75mg/m^2 body surface area every day for 7 days, followed by three weeks without treatment (28-day treatment cycle). In case of local problems at the injection site, intravenous treatment is also easily feasible. A full course of treatment should consist of a minimum of six cycles and should be continued as long as the patient continues to benefit or until disease progression is stopped [1].

subcutaneous injections are administered for 7 days, for at least 6 cycles

Prior to every treatment cycle, laboratory blood tests (complete blood counts, liver function, serum creatinine) should be performed [1].

2 Indication

Azacitidine (Vidaza®) is indicated for the treatment of intermediate-2 and high risk MDS (according to International Prognostic Scoring System (IPSS)), chronic myelomonocytic leukemia and acute myeloid leukaemia in adults who are not eligible for haematopoietic stem-cell transplantation.

indicated for intermediate-2 and high risk MDS in adults who are not eligible for haematopoietic stem-cell transplantation

3 Burden of disease

MDS are caused by dysfunctions of the bone marrow and can progress to acute myeloid leukaemia

Myelodysplastic syndromes (MDS) are caused by dysfunctions of the bone marrow and might develop de-novo or as a secondary MDS after chemotherapy or radiation therapy for other diseases [2]. The inability of the bone marrow to produce mature blood cells results in cytopenia of one or more of the peripheral blood cells and in an increasing number of bone marrow blast cells – factors which relate directly to the prognosis [3]. Symptoms include anaemia, repeated infections or bleeding. About one third of patients suffering from MDS progress to acute myeloid leukaemia (AML) [3].

By reasons that MDS comprise a heterogeneous group of conditions different classification schemes, mainly based on the cellular morphology, are in use, such as the French-American-British Classification (FAB) or the World Health Organization's (WHO) classification [2]. To assess the individual risk, the IPSS discriminates four risk groups. Based on number of cytopenia, percentage of marrow blasts and karyotype different prognoses for survival and transformation to AML can be made for each risk-group [3].

incidence estimates range from 3.3 to 5 per 100,000 people

No data is available on the overall incidence of MDS in Austria but estimates from other countries range from 3.3 [4] to 5 per 100,000 people per year [5]. Applied to an Austrian population of 8,355,000 [6], an estimated 275 to 420 persons per year would be affected. Due to a constantly increasing elderly population stratum this number is likely to increase in the near future.

median survival is between 0.4 and 5.7 years

According to the IPSS, individual prognosis depends on the risk-group with a median survival (without therapy) ranging from 0.4 years to 5.7 years [7]. The research group which had developed the IPSS based their findings on 816 patients. Within this study population they found that 22% of MDS patients had an intermediate-2 risk and 7% had a high risk MDS.

The median age of diagnosis is about 70 to 75 years [4] with 90% of patients aged over 60 years at the time of diagnosis. In individuals over 70 years the incidence rises to between 22 and 45 per 100,000 population per year [3].

4 Current treatment

Treatment options for intermediate-2 and high-risk MDS patients comprise

treatment options are:

- Supportive care: transfusion of red blood cells or platelets; antibiotic therapy and prophylaxis to treat infections, and iron chelation.

supportive care,

- Low dose chemotherapy (ARA-C, hydroxyurea, low dose melphalan).

low dose chemotherapy,

- Allogeneic hematopoietic stem cell transplantation (HSCT) is the single available curative treatment option and should be offered as first-line therapy to eligible patients [8, 9]. Due to an increasing risk of treatment-related mortality with increasing age, mainly younger patients are eligible [2]. However, modern concepts such as the use of dose reduced conditioning *"mini-allo tranplantation"* have moved generally accepted age limits for allogeneic transplantation up to 70 years in selected patients.

allogeneic hematopoietic stem cell transplantation,

- High-intensity chemotherapy for eligible patients lacking a stem cell donor or to reduce marrow blast counts.

high-intensity chemotherapy,

- The use of haematopoietic growth factors (erythropoietin (off-label), granulocyte-colony stimulation factor).

haematopoietic growth factors

- Decitabine, only as off-label use, either for patients who are not eligible for intensive therapy or as bridge to transplant if no donor is available [3].

decitabine

5 Current regulatory status

The European Medicines Agency (EMEA) granted market authorization for azacitidine in December 2008. Indications comprise the treatment of adults, if they are not eligible for bone marrow transplant and with:

EMEA market authorization for some MDS subtypes

- intermediate-2 and high risk MDS according to the IPSS,
- chronic myelomonocytic leukaemia (CMML) with 10% to 29% marrow blasts without myeloproliferative disorders,
- AML with 20% to 30% blasts (formerly known as refractory anaemia with excess blasts in transformation) and multi lineage dysplasia, according to the WHO classification [1].

For MDS orphan medicinal product designation was granted in February 2002 and for AML in November 2007.

The United States Food and Drug Administration (FDA) has granted market authorization for all MDS FAB subtypes in 2004 [10].

FDA approved for all MDS subtypes

6 Evidence

one phase III study, one phase II study and a retrospective analysis were identified

The evidence identified for this report comprises one phase III study, one phase II study and one retrospective analysis based on three trials. Additionally, one previous horizon scanning report on azacitidine was identified [11].

The phase III trial showed improved overall survival of patients with higher-risk MDS treated with azacitidine in comparison to the three other treatment regimens. Similarly, time to AML progression and haematological response were more favourable for the azacitidine group. The phase II trial compared different dosing regimens of azacitidine in patients with lower-risk MDS. All three treatment arms showed haematological improvements and increased transfusion independence. The retrospective reanalysis found increased median survival time for AML patients; response rates were observed in between 40% and 47% of all patients treated with azacitidine.

The most common side-effects were, according to the National Cancer Institute's Common Toxicity Criteria, grade 3 or 4 haematological reactions (in up to 91% of patients). Rare but severe side-effects leading to death were sepsis and bleeding.

6.1 Efficacy and safety - Phase III studie

Reference	NCT00071799, Published [12]
Sponsor	Celgene Corporation
Country	Europe
Design	Randomized, open label, active control
Participants characteristics	358 pts1 (I 179 vs C 179), median age: 69 years (range: 38 – 88 years)
Treatments	I(ntervention): azacitidine subcutaneous at 75mg/m² per day for 7 days every 28 days for at least 6 cycles; treatment was continued until study completion (12 months after last patient was assigned) or discontinuation due to unacceptable toxicity, relapse, or disease progression C(onventional care as control group): - best supportive care - low-dose cytarabine - intensive chemotherapy (induction with cytarabine + daunorubicin/idarubicin or mitoxantrone)
In-/exclusion criteria	Pts with higher-risk MDS - RAEB, RAEB-t or CMML (FAB Classification)[2] Exclusion of pts with therapy-related MDS, previous azacitidine treatment or planned allogeneic stem-cell transplantation
Follow-up	Until death or study completion

[1] *pts = patients*

[2] *RAEB = Refractory Anaemia with Excess Blasts, RAEB-t = Refractory Anaemia with Excess Blasts in Transformation; CMML = Chronic Myelomonocytic Leukaemia*

Outcomes	Primary: overall survival Secondary: time to transformation to AML, haematological response, independence from red-blood-cell transfusions, infections requiring antimicrobials, occurrence of adverse effects
Key results (in comparison to conventional care group)	Overall survival at median follow-up of 21.1 months: I 24.5 months vs C 15 months (p=0.0001); HR[3]=0.58 (95% CI[4] 0.43 – 0.77); at 2 years: I 50.8% vs 26.2% (p< 0.0001) Median time to AML transformation: I 17.8 months vs C 11.5 months; HR= 0.5 (95% CI 0.35 – 0.70; p< 0.0001) Haematological response: Any remission: I 29% vs C 12% (p=0.0001) Complete remission: I 17% vs C 8% (p=0.015) Partial remission: I 12% vs C 4% (p=0.0094) Rate of infections treated with antimicrobials (per patient/year): I 0.6 vs C 0.92; RR[5]= 0.66 (95% CI 0.49 – 0.87; p=0.0032)
Adverse effects	Deaths overall: I 46% vs C 63%, deaths during first 3 months I 11% vs C 9% Neutropenia: I 91% vs C 76%, Thrombocytopenia: I 85% vs C 80%, Anaemia: I 57% vs C 68% Other, non-haematological adverse effects: site reactions, nausea, vomiting, fatigue, diarrhoea with azacitidine
Commentary	No significant difference between azacitidine and intensive chemotherapy group in all outcome measures, except lower rates of infections for azacitidine, possible explanation: small number of patients

[3] *HR = Hazard Ratio*
[4] *CI = Confidence Interval*
[5] *RR = Relative Risk*

azacitidine was compared to conventional care regimens in 358 patients

This randomized controlled trial focused on patients with higher-risk MDS. By reason that three different treatment regimens acted as control, investigators determined, according to age, general condition and comorbidities, which conventional care treatment was most suitable for each individual patient before randomization. Patients were then randomly allocated one-to-one to either azacitidine or conventional care regimens. Although overall baseline characteristics were well-balanced, some differences occurred within the three subgroups: as expected, patients in the high-intensity chemotherapy group were younger, had better clinical performance status and higher-risk disease. Nevertheless, the majority of patients were allocated to the best supportive care group, suggesting that patients were representative of those where high-intensity treatments or stem-cell transplant were no treatment options.

overall survival was extended by 9.5 months in the azacitidine group

Overall survival of patients treated with azacitidine in comparison to the three most common therapy regimens was extended by 9.5 months. No differences were found in time to AML progression when comparing azacitidine and low-dose cytarabine or intensive chemotherapy.

but not superior to intensive chemotherapy

Furthermore, a subgroup analysis of azacitidine in comparison to intensive chemotherapy showed lower rates of infections for the azacitidine group but failed otherwise to demonstrate improved outcomes. Based on the fact that complete remission was achieved more often in the high-intensity chemotherapy group (in 36% of pts) than in the azacitidine group (in 29% of pts), the authors conclude that high-intensity chemotherapy prior to stem-cell transplantation might result in a better and faster reduction of bone marrow blasts than azacitidine.

four treatment related deaths

Deaths observed in 82 patients (46%) in the intervention group and in 113 patients (63%) in the control groups were considerably high. Of those, however, only four deaths in the azacitidine group (due to sepsis and bleeding) and one in the control group are believed to have been treatment related.

haematologic side-effects were very common

Very common haematologic side-effects, most often responsible for treatment discontinuation, were neutropenia, thrombocytopenia and anaemia, but independence from red-blood-cell transfusion as well as rate of infections requiring antimicrobials showed favourable outcomes for azacitidine.

6.2 Efficacy and safety - further studies

a phase II trial of patients at lower-risk MDS showed hematologic improvements

A phase II multicenter, randomized trial evaluated the impact of three different dosing regimens in a total of 151 patients [13]. The study population consisted mainly of patients with FAB lower-risk or RAEB. Hematologic improvement was observed in 44% to 56% of patients and transfusion independence was achieved in 50% to 64% patients. Within the six-cycle treatment phase adverse effects were neutropenia (38%), anaemia (29%), thrombocytopenia (25%) and leukopenia (18%). Non-haematological side-effects encompassed fatigue, nausea, erythema at the injection site and constipation. Out of three patients who died during treatment, one death is believed to have been treatment-related.

retrospective analysis demonstrated prolonged median survival

Another publication reanalysed data of three trials, one randomized controlled trial where patients were allowed to cross-over after 4 months and two trials with only one arm [14]. Of a total of 309 patients, 286 had been treated with azacitidine and out of those 48 had received the drug intravenously. Across all azacitidine arms a treatment response (defined as complete/partial remission or haematological improvements) was observed in 40% to 47% of patients. A subgroup analysis of AML patients who had been participating in the randomized controlled trial showed a median survival time of 19.3 months in the intervention group compared to 12.9 months in the control group. Improvements in platelet and red blood cell transfusion were more often achieved in the active treatment arm. Adverse effects, including haematologic and non-haematologic effects were seen more frequently in the control group than in the intervention group.

7 Estimated costs

6 cycles cost EUR 32,000

One vial of Vidaza® 100mg suspension for injection is approximately € 381 (manufacturer's price) [15]. Therefore, one course of treatment (6 cycles) is expected to be around € 32,000 (assuming an average body surface area of $1.7m^2$ and therefore using 2 vials per day). These costs are alternatively to costs for other available treatment options for patients with intermediate-2 to high-risk MDS, such as allogeneic hematopoietic stem cell transplantation or high-intensity chemotherapy [3].

One has to bear in mind that Vidaza® treatment in responders is usually given continuously until disease progression or dose limiting toxicity occurs, but will be adapted often to individual patients' needs after the first cycles.

Therefore, a considerable proportion of patients will be on treatment for long periods of time.

8 Ongoing research

Three further phase III trials are currently enrolling patients:

further studies for different indications are ongoing

NCT00454480: will assess different chemotherapy regimens (including azacitidine) with combinations of monoclonal antibodies for the treatment of MDS and AML. First results can be expected in August 2012.

NCT00887068: will evaluate the use of azacitidine after allogeneic transplantation and is scheduled until April 2014.

NCT00422890: azacitidine for the treatment of the haematological relapse in patients suffering from AML or MDS with falling CD34-chimerism after haematopoietic stem cell transplantation. Primary completion date is expected to be January 2010.

Additionally, plenty of phase I and phase II trials are ongoing or recruiting patients. Research areas include azacitidine for patients with low-risk MDS, in combination with other treatment options for the management of MDS/AML or azacitidine prior to stem-cell transplantation in high-risk MDS [16] and fullblown AML.

9 Commentary - English

Based on the promising results of mainly one phase III study which demonstrated increased survival rates for intermediate-2 to high-risk MDS patients in comparison to three other forms of treatment, European Union-wide market authorization was granted by EMEA in December 2008 [1].

EMEA granted market authorization for intermediate-2 to high-risk MDS in 2008

So far, treatment options for higher-risk MDS patients included therapies such as high-intensity chemotherapy and allogeneic HSCT [3]. However, eligibility for these treatment regimens depends on age, co-morbidities and clinical performance, hence only a limited number of patients are suitable. Thus, azacitidine provides a valuable treatment option for these difficult to treat MDS patients and has consequently found its way into daily clinical practice in Austria. Nevertheless, data assessing azacitidine under real-life conditions are missing, emphasizing the need for pragmatic trials conducted by independent institutions and comparing azacitidine to, for example, conventional chemotherapy regimens.

so far, only limited treatment options available, azacitidine a valuable alternative

Although decitabine, an azacitidine congener, can theoretically be used off-label for the treatment of MDS patients, data from randomized phase III trials reporting survival benefit for individuals treated with this drug are still missing [3].

haematologic side-effects common

Most commonly reported side-effects of azacitidine are haematologic reactions occurring during the first two treatment cycles. Treatment options and preventive measures include monitoring of complete blood count, prophylactic antibiotics, delay of azacitidine administration or red-blood-cell transfusions [1].

As subcutaneous administration provides an easy way of treatment delivery, self-administering at home is feasible [17]. Additionally, a phase I trial is recruiting participants to assess the oral application of this drug which might facilitate its application even further [16].

already off-label use in Austria

It is likely that azacitidine will be used more frequently in the near future: the FDA has approved the drug for all FAB-subtypes [10], the National Comprehensive Cancer Network has incorporated azacitidine into its clinical practice guidelines for low-risk MDS patients as well as for patients who relapse after stem-cell transplant [3] and more studies to assess its value prior to/ after transplantation are under way. Therefore, off-label use in Austria is already going on.

economic consequences unclear

The economic consequences are unclear. On the one hand, by reasons that treatment should be continued as long as patients experience benefit or the disease does not progress [1] and combined with the potential of a more widespread use for broader indications (e.g. low risk MDS, stem-cell transplant, AML in the elderly), costs might be considerable. On the other hand, increased transfusion independence and the self-administration at home could lead to a reduced use of in-patient services and therefore to cost savings. If the costs have to be borne mainly by hospital providers or will occur in the out-patient sector will depend on the presence of oncologists in own practices – a condition practically absent in Austria.

10 Commentary - German

EMEA Zulassung für mittleres Risiko 2 und hohes Risiko MDS

Basierend auf den Ergebnissen einer Phase III Studie, die ein verlängertes Gesamtüberleben für MDS PatientInnen mit mittlerem Risiko 2 und hohem Risiko nach IPSS im Vergleich zu konventionellen Therapieformen gezeigt hatte, erhielt Azacitidine im Dezember 2008 von der EMEA die europaweite Marktzulassung [1].

nur wenige Therapieoptionen vorhanden

Therapien für Hochrisiko MDS PatientInnen, wie Stammzelltransplantation oder intensive Chemotherapie, stellen nur für eine sehr limitierte PatientInnengruppe eine Behandlungsoption dar, weil nur jüngere PatientInnen und Personen mit gutem Allgemeinzustand für diese Therapien geeignet sind [3]. Azacitidine bietet nun für diese vormals schwierig zu behandelnden PatientInnen eine wertvolle Therapiealternative dar und hat daher in Österreich bereits Eingang in den klinischen Alltag gefunden. Nichtsdestotrotz, Daten zur Wirksamkeit unter Realbedingungen sind noch ausständig, wobei vor allem pragmatische Studien von unabhängigen Institutionen, die Azacitidine mit herkömmlichen Chemotherapien vergleichen, wünschenswert wären.

Azacitidine bietet Alternative

hämatologische Reaktionen häufig

Obwohl zwar mit Decitabine generell ein ähnliches Produkt, wenn auch nur im „Off-label“ Gebrauch, zur Verfügung stehen würde, sind Daten aus ran-

domisierten Phase III Studien, die ebenfalls ein verlängertes Gesamtüberleben beweisen würden, für dieses Medikament noch ausständig.

Die häufigsten beobachteten unerwünschten Nebenwirkungen von Azacitidine waren hämatologische Reaktionen während der ersten beiden Behandlungszyklen. Vorsichtsmaßnahmen und Behandlungsoptionen für diese Nebenwirkungen beinhalten unter anderem regelmäßige Laborkontrollen, Gabe von Erythrozytenkonzentraten oder Antibiotika.

Die subkutane Injektion von Azacitidine stellt eine unkomplizierte Art der Verabreichung dar und bietet PatientInnen auch die theoretische Möglichkeit, sich den Wirkstoff selbst zu Hause zu verabreichen [17]. Die Einnahme dieses Medikaments könnte eine weitere Vereinfachung erfahren, weil die orale Gabe bereits Gegenstand weiterer klinischer Studien ist [16].

off-label Gebrauch in Österreich

Dass Azacitidine, zunächst für off-label und in weiterer Zukunft für ausgeweitete Indikationsstellungen verwendet werden wird, ist sehr wahrscheinlich, zumal die FDA Azacitidine für alle FAB- Subtypen zugelassen hat [10], das „National Comprehensive Cancer Network" Azacitidine in seinen Guidelines auch für die Behandlung von Niedrigrisiko MDS Patientinnen inkorporiert hat [3] und weitere Studien den Nachweis erbringen sollen, dass der Einsatz dieses Medikaments auch vor/nach Stammzelltransplantationen und im Rahmen der AML Therapie gerechtfertigt ist.

Kostenkonsequenzen unklar

Die Kostenkonsequenzen sind unklar. Auf der einen Seite könnten die anfallenden Ausgaben beträchtlich sein – vor allem bei Indikationsausweitungen, der zunehmenden MDS Inzidenz und bedingt dadurch, dass die Therapie fortgesetzt werden soll, solange PatientInnen davon profitieren und die Krankheit nicht fortschreitet [1]. Auf der anderen Seite könnte es durch den verminderten Transfusionsbedarf und durch die Möglichkeit der Selbstverabreichung zu einer verminderten Inanspruchnahme von stationären/ambulanten Aufenthalten kommen. Ob die Kosten letztlich hauptsächlich von Krankenhausträgern zu bezahlen sein werden, wird von der Verfügbarkeit niedergelassener Onkologen abhängen – eine Bedingung die in Österreich praktisch nirgends erfüllt ist.

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